REMARKS

Claims 99-107, 109-117, 119 and 121-127 were previously pending. Applicants have canceled claims 101-102, 111-112 and 122-127 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended claim 99 to recite "wherein each cytosine in said oligonucleotide is a 5-methylcytosine." Support for this amendment can be found throughout the specification as filed, for example, at page 62, lines 24-28. Applicants have amended claims 107, 117 and 121 in view of the amendment of claim 99. Applicants submit that no new matter is added and request entry of these amendments. After entry of these amendments, claims 99-100, 103-107, 109-110, 113-117, 119 and 121 will be pending and under consideration.

35 U.S.C. § 103(a) – Obviousness

Claims 99-107, 109-119 and 121-127 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nyce *et al.*, (WO 96/40266) in view of Nicklin *et al.* (WO 98/09633) and Levesque *et al.*, (Mol. Pharmacol., 51, 1997, 209-216). *Office Action* at 4. The Office asserts that Nyce discloses the invention with the exception of 2'-O-methoxyethyl and 5-methylcytosine modifications. *See Office Action* at 6. The Office asserts that Nicklin and Levesque disclose the missing elements, that it would have been obvious to modify the antisense of Nyce to include the modifications of Nicklin and Levesque, and that the level/degree of modification amounts to routine optimization. Applicants respectfully traverse.

Applicants submit that the Office has failed to establish a *prima facie* case of obviousness for the reasons previously articulated. Specifically, given the number of modifications disclosed in Nicklin, and the fact that Nicklin discloses that one of the "especially preferred embodiments" is one which contains no 2'-modified nucleotides (*Nicklin* at 4), Appellants submit that the instant case is one in which what is obvious to try is "to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave ... no direction as to which of many possible choices is likely to be successful." *O'Farrell*,

853 F.2d at 903 (emphasis added). As such, "obvious to try" in the instant case cannot be equated with obviousness under 35 U.S.C. § 103(a).

In addition, even if a *prima facie* case of obviousness has been established, a point which Applicants do not concede, Applicants submit that the claimed method provides unexpected results. Applicants have found that incorporating 2'-O-methoxyethyl (2'-MOE) and 5-methylcytosine nucleosides improves the uptake of oligonucleotides into cells of the lungs. Tables 2 and 3 of Example 3 show the concentration of oligonucleotide in the lungs of mice following single and multiple administrations, respectively, of three antisense molecules. Importantly, ISIS 15163 performs more than 3 times better than ISIS 17009.

As the Office has correctly noted, ISIS 15163 contains 2'-O-methoxyethyl and 5'-methylcytosine nucleosides, while ISIS 17009 does not. Applicants previously incorrectly stated that the only difference between the molecules was the inclusion of 2'-O-methoxyethyl nucleosides in ISIS 15163. Applicants apologize for this error.

The fact that oligonucleotides with 2'-O-methoxyethyl and 5-methylcytosine modifications have improved pulmonary uptake is clearly unexpected in view of the cited references, which do not teach that 2'-O-methoxyethyl or 5-methylcytosine modifications improve cellular uptake.

The Office has responded by arguing that Nicklin teaches that 2'-MOE and 5'-methylcytosine modifications "confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target." *Office Action* at 9. Specifically, the Office relies on the last paragraph on page 2 of Nicklin to support the assertion that modifications confer one or more properties including "increased nuclease resistance, or increased uptake to cells, [and] increased binding affinity for the RNA target." *Office Action* at 10.

Applicants respectfully submit that Nicklin does not support this assertion. The cited portion of Nicklin reads in part:

> In some preferred oligonucleotides (A), at least one nucleotide is modified at the 2' position of the sugar moiety. Certain preferred oligonucleotides (A) are chimeric oligonucleotides. "Chimeric oligonucleotides" or "chimeras", in the context of this invention, are oligonucleotides which contain two or more chemically distinct regions, each made up of at least one nucleotide. These oligonucleotides typically contain at least one region of modified nucleotides that

> confers one or more beneficial properties (such as, for example, increased nuclease resistance, increased uptake into cells, increased binding affinity for the RNA target) and a region that is a substrate for RNase H cleavage. In one preferred embodiment, a chimeric oligonucleotide comprises at least one region modified to increase target binding affinity and, usually, a region that acts as a substrate for RNase H. Affinity of an oligonucleotide for its target is routinely determined by measuring the Tm of an oligonucleotide/target pair, which is the temperature at which the oligonucleotide and target dissociate; dissociation is detected spectrophotometrically. The higher the Tm, the greater the affinity of the oligonucleotide for the target. In a more preferred embodiment, the region of the oligonucleotide which is modified ***to increase target binding affinity*** comprises at least one nucleotide modified at the 2' position of the sugar, particularly a 2' -alkoxy, 2'- alkoxyalkoxy or 2'-fluoro-modified nucleotide. Such modifications are routinely incorporated into oligonucleotides and these oligonucleotides have been shown to have a higher Tm (i.e., higher target binding affinity) than 2'-deoxyoligonucleotides against a given target. *Nicklin* at page 2-3 (emphasis added).

This paragraph from Nicklin is first speaking of chimeric oligonucleotides generally, stating that "modified nucleotides" provide benefits "such as, for example, increased nuclease resistance, increased uptake into cells, increased binding affinity for the RNA target" – no specific modifications are mentioned with respect to these properties. Nicklin then continues, stating that chimeric oligonucleotides preferably comprise a region modified "to increase target binding affinity." Specifically, Nicklin states that the region modified "to increase target binding affinity" comprises a 2'-sugar modification. The discussion of 2'-sugar modifications only discusses affinity, never mentioning increased cellular uptake – there is simply no support for the Office's assertion that Nicklin teaches that 2'-MOE or 5'-methylcytosine leads to increased uptake in cells.

In fact, increased cellular uptake is only mentioned twice in Nicklin – in the last paragraph of page 2, as shown above, and the second paragraph of page 2, which states:

> As used in the context of this invention, the term "oligonucleotide" refers to a substance having a plurality of nucleotide units formed from naturally occurring bases and sugars joined by phosphodiester internucleoside (backbone) linkages. The term "oligonucleotide" also includes analogues which function similarly to naturally occurring oligonucleotides but which have non-naturally occurring monomers (nucleotides) or portions thereof. These oligonucleotide analogues are often preferred over native forms because of properties such as enhanced cellular uptake, enhanced target binding affinity and increased stability in the presence of nucleases. *Nicklin* at 2 (emphasis added).

Again, this passage only discusses oligonucleotide analogues generally – no specific modifications are mentioned. Thus, while Nicklin may disclose that 2'-sugar modifications are desirable for increasing target binding affinity, there is no teaching that this modification would increase cellular uptake.

In addition, 5'-methylcytosine modifications are only mentioned once: "Other preferred embodiments may include at least one modified base form or 'universal base' such as inosine. Preferred bases include xanthine, hypoxanthine, adenine, 2-aminoadenine, guanine, 6-thioguanine, uracil, thymine, cytosine, 5-methylcytosine, 5-propynyluracil, 5-fluorouracil and 5-propynylcytosine." *Nicklin* at 4. Thus, contrary to the Office's assertion that Nicklin teaches that 2'-sugar modifications or 5-methylcytosine modifications increase uptake, Nicklin never mentions that these modifications increase cellular uptake.

The fact that one of skill in the art at the time of the invention would not believe that 2'-sugar modifications would improve cellular uptake based on Nicklin is supported by the expert declaration of Dr. Richard Geary, previously attached as Exhibit 1. In paragraph 4 of his declaration, Dr. Geary states:

> I have reviewed Nicklin et al. and do not find support for the assertion that incorporation of 2'-O-methoxyethyl modifications would result in increased uptake of a nucleic acid into cells. The specific section of Nicklin asserted to teach that modifications of antisense oligonucleotides confer increased uptake into cells does not suggest that 2' modifications are capable of increasing cellular uptake. Rather, Nicklin et al. confirm, as was understood at the time, that modifications of the 2' position of the nucleotide sugar increases target binding affinity. *Nicklin* at pages 2-3.

Further, Dr. Geary states that "at the time of the invention, one in the field would not have expected the inclusion of 2'-O-methoxyethyl modifications to improve the uptake of nucleic acids into a cell of the lung." *Geary Declaration* at ¶5 (emphasis added).

In response to this expert declaration, the Office states that the declaration "does not negate the motivation to incorporate such modifications [2'-MOE] to confer increased nuclease resistance, increase uptake into cells, and increase binding affinity for the RNA target, wherein there is a reasonable expectation that incorporation of at least one of such modifications would likely add some benefit given that such modifications are taught to add such benefits." *Office Action* at page 12, (emphasis added).

Applicants respectfully submit that the Office's response is flawed for three reasons. First, as demonstrated above, Nicklin does not teach the inclusion of 2'-O-methoxyethyl to confer "increased uptake into cells" – this assertion is unsupported by the reference.

Second, the assertion that inclusion of at least one 2'-O-methoxyethyl modification would likely add "some benefit" does not address the question of whether the cited references teach that 2'-O-methoxyethyl modifications were expected to improve cellular uptake. The fact that 2'-sugar modifications may have been expected to increase target binding affinity does not mean that increased cellular uptake is not an unexpected result.

Third, the assertion that the declaration does not "overcome the motivation" to include these modifications implies that unexpected results must negate any motivation to include the recited modifications – that is not the purpose of citing to unexpected properties. Unexpected properties do not negate motivations to include modifications, they overcome any *prima facie* case that it was obviousness to include the modifications by establishing that the modifications worked better or were superior in a way that is unexpected in view of the cited references. The expert declaration of Dr. Geary establishes that increasing cellular uptake is an unexpected benefit of the recited 2'-sugar modifications in view of Nicklin and the state of the art.

In an apparent attempt to suggest that the expected increased binding affinity resulting from including 2'-sugar modifications would also result in increased cellular uptake, the Office makes the unsupported assertion that "an increased binding affinity would be expected to enhance cellular uptake, as these events are not mutually exclusive." *Office Action* at 10.

Applicants respectfully submit that it is not well known in the art that "increased binding affinity would be expected to enhance cellular uptake." The fact that they are not mutually exclusive is not support for this conclusion – it simply means that they can both occur at the same time, not that one is expected to lead to the other. Applicants are not aware of any reasoning that supports the conclusion that an increase in binding affinity of the oligonucleotide to its mRNA target – something which occurs after the oligonucleotide has entered the cell – would lead to an increase in uptake of the oligonucleotide into the cell. In the absence of any supporting evidence or reasoning, Applicants submit that the Office's assertion represents official notice without documentary evidence, and Applicants request documentary evidence in support of the noticed fact, in accordance with *In re Zurko*, 258 F.3d 1379 (Fed. Cir. 2001).

Finally, the Office asserts that the claims are not commensurate in scope with the asserted unexpected results because ISIS 15163 has 5-methylcytosines as well as 2'-MOE modifications. Without acquiescing to the Office's assertion, and solely in the interest of advancing prosecution, Applicants have amended independent claim 99, and thus all pending claims, to recite "wherein each cytosine of said oligonucleotide is a 5-methylcytosine."

In summary, Applicants submit that the cited references do not teach that the inclusion of 2'-sugar or 5-methylcytosine modifications would increase cellular uptake of an aerosolized oligonucleotide delivered into the lung and thus the results reported in the instant specification are unexpected. While the cited references may suggest the inclusion of 2'-sugar modifications for increasing binding affinity of the oligonucleotide to its target mRNA, and even *if* this provides motivation to include a 2'-sugar modification, the cited references do not render the use of a molecule including this modification obvious if the resulting methods have unexpected results. If a motivation to include a modification always negated unexpected properties that flowed from the modification, unexpected properties could never be the basis for overcoming a *prima facie* case of obviousness. Such a rule would clearly be contrary to the M.P.E.P. and caselaw. *See M.P.E.P. §2145* (stating the unexpected results can overcome a *prima facie* case of obviousness). Thus, even *if* the Office has established that one of skill in the art would have been motivated to include a 2'-sugar and 5-methylcytosine modification, a point Applicants do not concede, Applicants submit that the evidence of record establishes that the increased cellular uptake of the recited compounds is unexpected, and therefore the pending methods are not obvious.

For at least the above reasons, Applicants submit that the pending claims are patentable over Nyce, in view of Nicklin, and Levesque. Applicants therefore request withdrawal of the rejection of the pending claims under 35 U.S.C. § 103(a).

35 U.S.C. § 112 – New Matter

New claims 122-125 and 127 are rejected under 35 U.S.C. § 112, first paragraph, as containing new matter. Without acquiescing to the Office's rejection, and solely in the interest of advancing prosecution, Applicants have canceled claims 122-125 and 127 without prejudice to, or disclaimer of, the subject matter contained therein.

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 122-125 under 35 U.S.C. § 112, first paragraph.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents and Applications

Applicants wish to draw the Examiner's attention to the following patents or applications. Applicants encourage the Examiner to review and monitor the prosecution of the following patents and/or applications throughout the pendency of this application.

Patent / Serial Number	**Title**	**Issued / Filed**
09/083,586	COMPOSITIONS AND METHODS FOR THE PULMONARY DELIVERY OF NUCLEIC ACIDS	5/21/1998

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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